Shelby.Michael

From: Barone.Stan@epamail.epa.gov
Sent: Monday, July 8, 2002 6:13 PM
To: Shelby.Michael
Subject: public comments on CERHR methanol report
Importance: High

Dear Dr. Shelby,

I am glad to see this report has finally been released since it demonstrates a lot of work for all of the review panel. I do however, share many of the concerns that made me unable to sign the consensus statement of the final conclusions.

In brief my concerns relate to issues that originate in the review process and in the risk communication aspects of the final conclusions. I am still concerned that the process that led up to the final conclusions still misses the mark with respect to risk communication. I believe it is important to state clearly that the absence of data or uncertainties in the data do not signify a lack of risk as stated in the final conclusions of minimal and negligible risk.

The panel could not agree about the significance of the outcomes in the primate study of Burbacher et al., 1999 but the CERHR report's conclusions in essence sidestep this issue. I believe it is important to state when experts can not arrive at consensus about data that relates to risk communication. The panel agreed that the critical effects of methanol exposure were developmental effects and that the parent compound was the protoxicant. The panel also agreed that the metabolism of ethanol was sufficiently similar to ethanol. I continue to express concern that this similarity in metabolism, teratological outcomes in mice and the Burbacher study raises concern for more data on low dose exposure and effects on the developing nervous system at doses that do not produce overt teratology. I think more effort is needed in characterizing exposure and effects in potential susceptible populations. There is significant evidence that there are significant subpopulations that are at increased risk to ethanol's developmental toxicity due metabolic deficiencies that often arise from genetic polymorphisms that impair alcohol detoxification (e.g., alcohol dehydrogenase and specific P450 isoforms). This issue is mentioned in the CERHR report's conclusions but it is not explicitly noted as a critical data need for future risk assessment. The panel agreed the critical effects of methanol exposure were developmental effects in the fetus. It seems inconsistent that the fetus and child are the susceptible population which we are most concerned about but susceptible populations issues are not listed as a critical data for risk determination. This seems almost counter-intuitive, since we identified

the critical effect were adverse developmental outcomes. Who are the populations at risk should be an explicit part of the panel considerations.

Again, I reiterate that I do not think that the process that the panel went through for the evaluation of methanol adequately addressed susceptible populations concerns. I hope this issue will be discussed more extensively in future CERHR panel reports and will be included in the framework for all considerations of future chemical evaluations. What do we know was the featured question of the evaluation process with little or no emphasis on what we need to know about sensitive subpopulations in order to evaluate risk (e.g., pregnant women with genetic polymorphisms that limit detoxification capacity of methanol). I believe the panel needs more than one meeting to address all these issues and the ground rules of the meeting need to be more explicitly stated and discussed prior to the consideration of the final face to face meeting. This process could be revised with a conference call that allows for discussion of the ground rules, the process, and the goals of the process followed by a one day face to face meeting to discuss the data summaries prior to the concluding meeting where the critical studies are discussed and the conclusions and consensus or lack of consensus statement are worked out for the final report.

I believe the final NTP report can address some of these concerns.

Stanley Barone, Jr., Ph.D.
Research Biologist
Cellular and Molecular Toxicology Branch
Neurotoxicology Division/NHEERL/ORD
U. S. Environmental Protection Agency
86 T.W. Alexander Drive, MD 74B
Research Triangle Park, NC 27711
919-541-3916 (phone)
919-541-0546 (fax)